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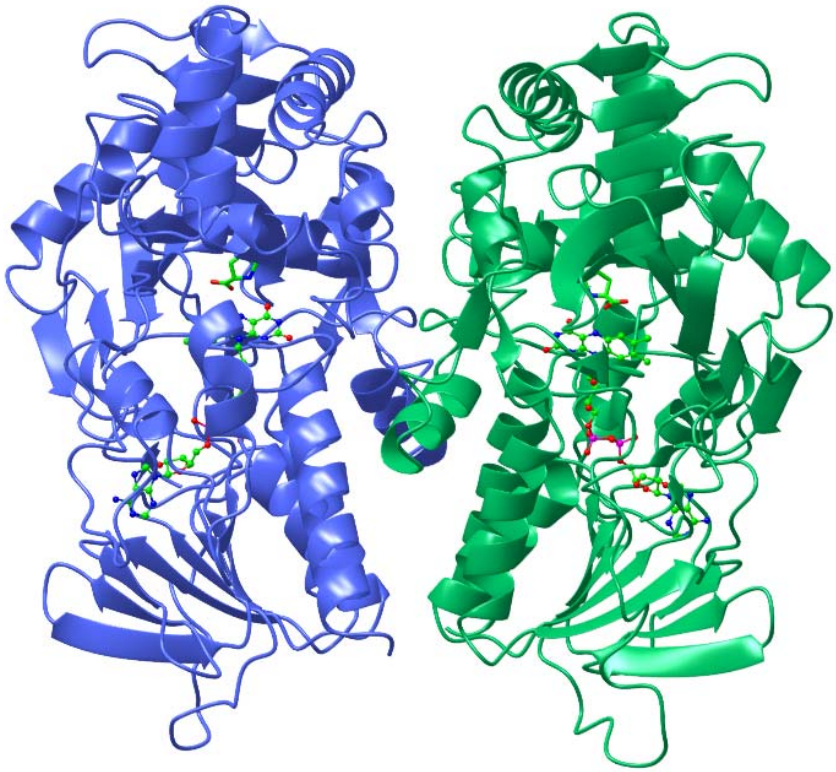

Silver catalyzed cascade synthesis of alkaloid ring systems: concise total synthesis of fascaplysin, homofascaplysin C and analogues†‡

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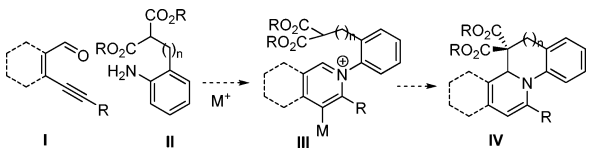
A silver catalyzed and microwave assisted one-pot cascade synthesis provides efficient access to diverse alkaloid-inspired scaffold classes, and a concise and efficient total synthesis of homofascaplysin C and fascaplysin.

Compound libraries based on natural product core scaffolds are an important source of bioactive molecules for medicinal chemistry and chemical biology research.[1] Efficient reaction sequences that give flexible access to scaffold and stereochemical diversity and complexity preferably employing catalytic multi-step synthesis sequences are in high demand.[2] In this respect the core scaffolds of alkaloid classes are particularly important since numerous alkaloids display diverse biological activities. Consequently the synthesis of alkaloid-inspired compound collections has received considerable attention.[3–4] Here we report the development of a silver-catalyzed cascade reaction sequence that gives access to different alkaloid-inspired polycyclic scaffold classes in an efficient one-pot process, including fascaplysin-type alkaloids and analogs thereof. For the development of the sequence we reasoned that an imine formed from an acetylenic benzaldehyde (I) and an aniline with a pendant nucleophile (II) would undergo cycloisomerization in the presence of Ag/Au ions as catalysts that activate the alkyne for nucleophilic attack to yield the isoquinolinium intermediate (III).[5,6] This cation would be subject to a nucleophilic attack from the pendant 1,3-dicarbonyl group to form scaffold IV (Scheme 1).

Structural variation of the acetylenic aldehyde and the nucleophile attached to the aniline would give rise to diverse ring systems fused to a common isoquinoline motif, which defines the core structure of a large group of biologically and medicinally relevant compounds.[7]



Scheme 1 Design of a cascade route to diverse alkaloid scaffolds.

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In initial exploring experiments, we investigated different reaction conditions using 2-(phenylethynyl)benzaldehyde **1a** and di-*tert*-butyl-2-(2-aminophenyl)malonate **2a** as substrates and Au(III), Au(I) and Ag-salts as catalysts (see Table 1). While the use of Au(I) did not lead to product formation, $AuCl_3$ either alone or in the presence of a silver co-catalyst induced formation of decarboxylated product **3a** (Scheme 2). The expected intermediate **6** could be isolated in low yield (<10%) and converted into **3a** in a separate transformation.

Further experiments revealed that $AuCl_3$ or AgOTf alone in dichloroethane or ethanol give only relatively low yields of **3a** (Table 1, entries, 2, 4, 5 and 7). Combination of $AuCl_3$ with a silver co-catalyst in dichloroethane resulted in a higher yield whereas in ethanol such a promoting effect was recorded only at higher temperature (Table 1, entries 3 and 6). A significant increase in yield was observed when 20 mol% of AgOTf was used at 60 °C in ethanol along with an excess of a nitrogen-base like proline or lutidine (Method A, Table 1, entries 8 and 9). Under these conditions the final product was formed in yields up to 84%. If the catalyst loading was lowered, the reaction did not go to completion even after two days. Finally, we explored whether microwave heating would accelerate the reaction sequence, and, gratifyingly, the desired product **3a** was isolated in 95% yield after irradiation at 150 °C (150 W) for 45 min in the presence of 2.5 mol% AgOTf and 10 mol% of lutidine (Method B; entry 1, Table 2). Under the optimized reaction conditions either with normal heating or with microwave heating, acetylenes carrying electron rich aromatic substituents and alkyl groups (Table 2, entries 2–4, and 6) yielded the corresponding indoloisoquinolines in high yields.

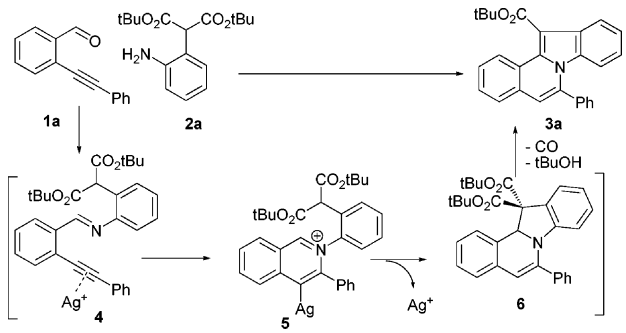
In general microwave heating enhanced the yields by up to 25% in these cases (**3a–3d**). Microwave heating proved to be particularly efficient if the acetylene was substituted with an aromatic ring carrying an electron-withdrawing group (Table 2, entries 5, 9, 12 and 16) or if the aniline carried electron-donating substituents (Table 2, entries 10–12). The most striking reactions were those between electron-rich aldehydes and electron-rich anilines which proceeded only under microwave heating (Table 2, entries 14–16). These results demonstrate that the developed Ag^+-catalyzed cascade sequence provides an efficient access to tetracyclic indoloisoquinolines **3** in a one-pot, four-step transformation. This heterocycle class is of particular importance due to its pronounced antitumor activity.[8]

In order to extend the scope of the cascade synthesis and to expand the scaffold diversity accessible by means of this method we employed indole- and furan-derived acetylenic aldehydes **7** (Scheme 3) in the silver catalyzed transformation. In these cases regular heating and microwave heating in the

Table 1 Cascade synthesis of indolo[2,1-*a*]isoquinolines[a]

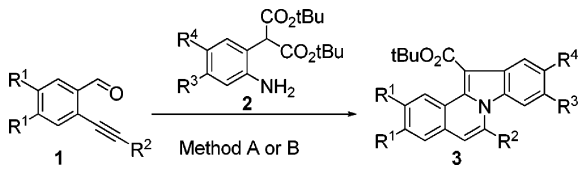
Entry	Catalyst[b] (mol%)	Co-catalyst or base (mol%)	Solvent	*T*/°C	Time/h	Yield (%)[c]
1	$Au(PPh_3)Cl$ (10)	—	DCE	rt	72	n.r.
2	$AuCl_3$ (10)	—	DCE	rt	72	11
3	$AuCl_3$ (10)	$AgSbF_6$ (10)	DCE	rt	72	40
4	AgOTf (10)	—	DCE	rt	72	8
5	AgOTf (10)	—	DCE	80	18	21
6	$AuCl_3$ (10)	AgOTf (10)	EtOH	60	24	33
7	AgOTf (10)	—	EtOH	60	18	33
8	AgOTf (20)	L-Proline (100)	EtOH	60	18	74
9	AgOTf (20)	2,6-Lutidine (100)	EtOH	60	24	84

[a] For details of catalyst and reaction conditions screening, see the ESI. [b] No product was formed in the absence of any catalyst. [c] Isolated yields.



Scheme 2 Cascade synthesis of indolo[2,1-*a*]isoquinolines.

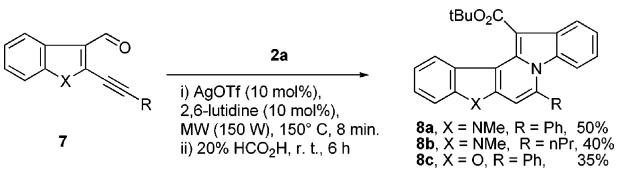
Table 2 Silver catalyzed synthesis of indolo[2,1-*a*]isoquinolines



Entry	No.	R^1	R^2	R^3	R^4	Yield[a] (%, A/B)[b,c]
1	**3a**	H	Ph	H	H	84/95
2	**3b**	H	3-Thiophene	H	H	81/92
3	**3c**	H	*n*-Pr	H	H	54/81
4	**3d**	H	3-OMe-Ph	H	H	64/85
5	**3e**	H	4-CF_3-Ph	H	H	13/56
6	**3f**	H	4-OMe-Ph	H	H	60/83
7	**3g**	OMe	Ph	H	H	50/78
8	**3h**	OMe	*n*-Pr	H	H	n.i./86
9	**3i**	OMe	4-CF_3-Ph	H	H	n.r./52
10	**3j**	H	Ph	OMe	OMe	21/65
11	**3k**	H	*n*-Pr	OMe	OMe	17/60
12	**3l**	H	4-CF_3-Ph	OMe	OMe	18/59
13	**3m**	H	Ph	OMe	H	n.i./87
14	**3n**	OMe	Ph	OMe	OMe	n.r./50
15	**3o**	OMe	*n*-Pr	OMe	OMe	n.r./73
16	**3p**	OMe	4-CF_3-Ph	OMe	OMe	n.r./67
17	**3q**	H	H	H	H	77/n.i.

[a] Isolated yields (n.r = no reaction; n.i. = not investigated). [b] Method A: AgOTf (20 mol%), 2,6-lutidine (1.0 equiv.), ethanol, 60 °C, 24 h; Method B: AgOTf (2.5 mol%), 2,6-lutidine (10 mol%), ethanol, MW-150 W, 150 °C, 45 min. [c] In isolated cases, remaining intermediate (tlc, LC-MS) was decarboxylated by treating the crude reaction mixture with 20% HCO_2H under reflux overnight to obtain the indolo[2,1-*a*]isoquinolines **3**.

presence of 2.5 mol% catalyst were ineffective. But the desired polycyclic products **8** were obtained in up to 50% overall yield in the presence of 10 mol% of the catalyst at a reaction time of



Scheme 3 Cascade synthesis of complex benzoindolizines.

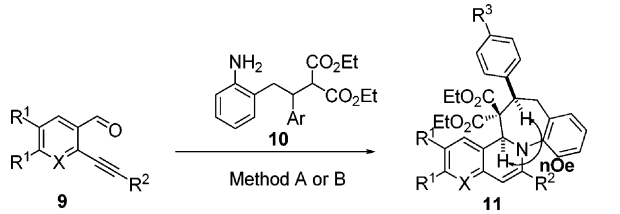
eight minutes followed by treatment of the crude reaction mixtures with 20% formic acid at room temperature to induce the decarboxylation.

Since aromatization appears to be the driving force for the decarboxylation to yield compounds **3** and **8**, we reasoned that increasing the length of the linker between the pendant nucleophile and the phenyl ring would prevent aromatization and lead to formation of larger ring systems with different scaffolds. To explore this possibility, aniline **10** with a substituted ethyl malonate moiety was treated with acetylenic benzaldehydes under the optimized reaction conditions for the silver catalyzed cascade cyclization. Gratifyingly, both alkyl and aryl substituted acetylenes including quinoline derivative **9c** (Table 3, entry 3) yielded the desired benzazepino[2,1-*a*]isoquinolines as single diastereomers in moderate to high yields (Table 3). The relative *cis*-configuration of **11a** was established by means of a clear nOe interaction between the two benzylic protons.

The successful implementation of the silver catalyzed cascade reaction sequence to skeletally diverse alkaloid-inspired ring systems encouraged us to apply this methodology to natural product synthesis. The fascaplysin- and homofascaplysin class of marine natural products[9] has a characteristic 12*H*-pyrido[1,2-*a*;3,4-*b*′]diindole pentacyclic framework which could readily be accessed using the silver catalyzed cascade cyclization reaction described above, thereby providing a concise synthesis of these natural products and possible analogues. The characteristic architecture of these molecules has previously inspired both total synthesis[10] endeavours and investigations into their biological activities.[11]

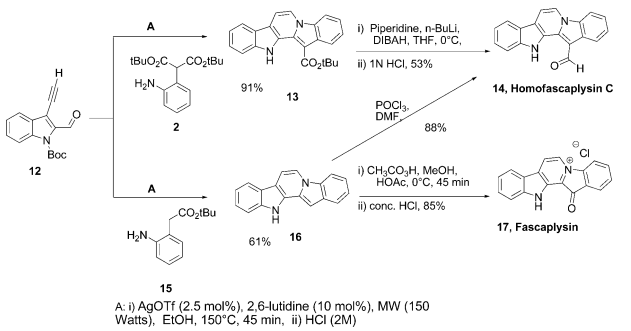
Boc-protected 3-ethynyl-indole-2-carbaldehyde (**12**) was employed as a common precursor for the natural product targets fascaplysin and homofascaplysin C. The microwave assisted silver catalyzed cascade cyclization of **12** with aniline **2** yielded the pentacyclic core **13** in high yield after acidic work-up (see the ESI‡). Partial reduction of the *tert*-butyl ester (~60% conversion) by means of *in situ* generated lithium diisobutylpiperidinohydroaluminate[12] provided the natural product homofascaplysin C (**14**) in 48% overall yield over four steps from **12** (Scheme 4).

Table 3 Silver catalyzed synthesis of benzazepeno[2,1-*a*]isoquinolines



Entry	No.	R^1	X	R^2	R^3	Yield[a] (%, A/B)[b]
1	**11a**	H	CH	Ph	H	72/89
2	**11b**	H	CH	^{n}Pr	H	58/82
3	**11c**	–Ph–	N	Ph	H	42/72
4	**11d**	H	CH	Ph	Et	75/90
5	**11e**	H	CH	3-OMe-Ph	Et	68/87
6	**11f**	H	CH	H	Et	59/n.i.
7	**11g**	OMe	CH	4-CF_3-Ph	Et	n.i./69

[a] Isolated yields (n.i. = not investigated). [b] Method A: AgOTf (20 mol%), 2,6-lutidine (1.0 equiv.), ethanol, 60 °C, 24 h; Method B: AgOTf (2.5 mol%), 2.6-lutidine (10 mol%), ethanol, MW (150 W), 150 °C, 45 min.



Scheme 4 Synthesis of homofascaplysin C and fascaplysin.

To overcome the difficult reduction of the *tert*-butyl ester **13** to final product **14**, aniline **15** was employed in the cascade synthesis of pentacyclic core **16** which was obtained in 61% yield.[13] Formylation of **16** with $POCl_3$ cleanly provided homofascaplysin C with an overall yield of 53%.[10a] In addition, the pentacyclic core **16** was efficiently transformed to the natural product fascaplysin by oxidation with peracetic acid, followed by salt formation in 52% overall yield (Scheme 4).[10a]

In conclusion we have developed an efficient one-pot, four-step silver catalyzed cascade sequence that gives ready access to a variety of skeletally diverse natural product inspired compound classes including fascaplysin-type alkaloids. This method will facilitate the synthesis and biological investigation of skeletally and structurally diverse alkaloid-based compound collections.

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